Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Thursday, August 09, 2018 4:29 PM
To: Jerry Campbell <JCampbell@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Kicking the tires…

I tested a couple of dose metric scripts. The mouse and rat ones I checked seem to produce values ('rout') almost exactly 50% of what's in the 'dose metrics' tab. But the human dose metric script matched.

```
> source('C:/Users/pschloss/Downloads/Desktop/chloroprene_fin/Human_dose_metric_2.R')
> rout
   ppm       AMP       AMPLU AMPK
1 12.3 0.2530232 0.04041056    0
2 32.0 0.6581998 0.10513844    0
3 80.0 1.6450145 0.26288161    0
> source('C:/Users/pschloss/Downloads/Desktop/chloroprene_fin/Male_rat_dose_metric_2.R')
> rout
   ppm       AMP      AMPLU       AMPK
1 12.3 0.4482158 0.1075722 0.06755752
2 32.0 1.1740539 0.2822177 0.09051064
3 80.0 2.9397783 0.7104413 0.10875550
```

There are no scripts to produce the plots sent by email (via Harvey) on 7/31. We will need them. It would be good to have plots for the kidney data/fits too, though it's a fairly small contributor.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Monday, August 06, 2018 9:30 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; cvanlandingham@ramboll.com; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

I was just getting to that option. See if this will work.

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 9:26 AM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Try just changing the file-extension from .zip to .txt and sending as an attachment. I'm trying to unzip the thing from the sharepoint site and just getting a spinning wheel.

From: Cynthia Van Landingham [mailto:cvanlandingham@ramboll.com]
Sent: Monday, August 06, 2018 9:19 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Unfortunately, I believe that the restrictions are on your end not ours. We can all see the files no problem.

Cynthia

Cynthia Van Landingham
Senior Managing Consultant

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M +1 (318) 6147920
cvanlandingham@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 8:18 AM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

I tried to just download it. Does it have to be this complicated? We'll be sharing with everyone as part of our open and transparent process…

-Paul

From: Cynthia Van Landingham [mailto:cvanlandingham@ramboll.com]
Sent: Monday, August 06, 2018 9:13 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Paul,
Did you download the zip file to your hard drive and then open or did you open it on the OneDrive site? If you did not try this, selecting all the files and allowing OneDrive to produce one download zip may be best. The

chloroprene_model.o_error.txt file is not in the zip we created so may be something that is being created due to the download process. Please read that file to find out if your IT security set-up is preventing files from being extracted.

Thanks, Cynthia

Cynthia Van Landingham
Senior Managing Consultant

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M +1 (318) 6147920
cvanlandingham@ramboll.com

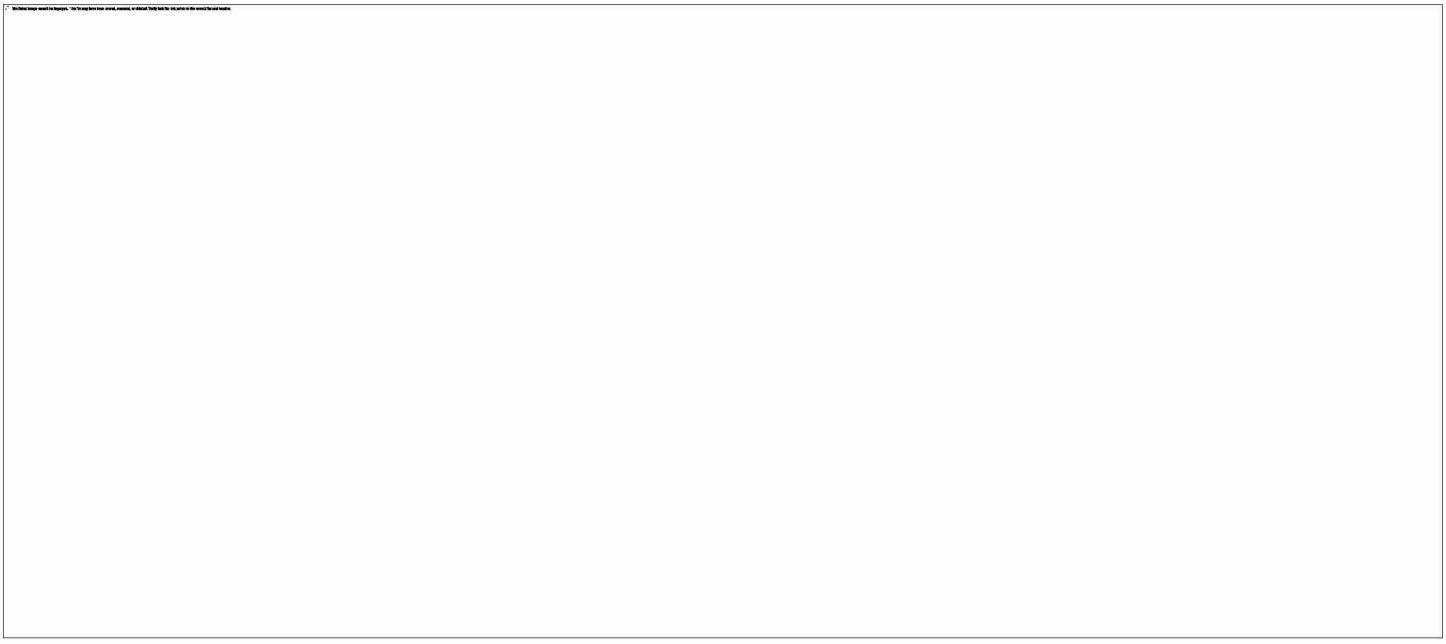
From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 7:53 AM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Harvey,

I sent a separate email to Alison. Below is a screenshot of the model folder that I got. There are none of the scripts listed in the Excel 'documentation' file.

Once we have those, give us some time to look at it. Hopefully it's easy enough to figure out, but we can let you and Jerry know if we need a walk-through.

-Paul



From: Harvey Clewell [mailto:HClewell@ramboll.com]
Sent: Friday, August 03, 2018 2:02 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Robinan Gentry <rgentry@ramboll.com>; cvanlandingham@ramboll.com; Allison Franzen

<AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: transmission of PBPK model for chloroprene

Hi Paul

As promised, we are providing you with the PBPK model for chloroprene written in R, with all the associated scripts and documentation. You should have received a separate email with an invitation to access the files on Microsoft OneDrive. Please let me if you have any problem downloading or opening them. Jerry Campbell would be happy to come over to EPA to help you set up the run environment in R studio and answer any questions you may have about running the model.

I'm looking forward to talking with you about the model and discussing any questions, suggestions, or concerns regarding it. Would it be possible to arrange an initial meeting sometime in the next few weeks. Miyoung Yoon is completing her review of the metabolism parameter scaling approach and I would like to be able to include you in the discussion of her recommendations.

Harvey Clewell

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MEMO DATE: September 5, 2018

To: Matthew Himmelstein

DuPont Haskell Global Centers
Newark, DE 19714

Subject: In Vitro Studies of Chloroprene Metabolism

From: Paul M. Schlosser, U.S. EPA

This memo is to request additional information and clarification regarding experimental studies conducted at DuPont Haskell Global Centers (previously Haskell Laboratory for Health and Environmental Sciences) to measure the oxidative metabolism of chloroprene (CP) using microsomes derived from liver and lungs of mice, rats, and humans, as described in Himmelstein et al. (2004) and Yang et al. (2012). The information (data) will assist in evaluation of the resulting mathematical models of the in vitro system, the parameters from which are being considered for use in a chloroprene PBPK model.

There are three data elements that I am seeking, described from highest to least priority.

1) Data regarding the mass-transfer resistance for movement of chloroprene between the headspace and the incubation medium

   One possibility are data demonstrating that under conditions of highest CP metabolic activity (concentrations below metabolic saturation) the rate of metabolism is linear with microsomal content; i.e., data showing the initial rate of clearance from the headspace doubles when the microsomal content is doubled or reduced by 50% when microsomal content is likewise reduced.

   Alternately, data where the rate of partitioning of CP between the headspace and incubation medium has been measured, starting immediately after the CP is introduced to the vial, until air-

medium equilibrium is reached. Such data are distinct from those used to determine the rate of system loss in the absence of metabolic activity after equilibrium is reached.

2) Clarification on headspace sample volumes used in the Himmelstein et al. (2004) study

In Himmelstein et al. (2004), p. 19, right column, last few lines, the methods description indicates that the head-space sample size for the CP oxidation experiments was 400 μL. In the computational scripts received the sample volumes for the corresponding experiments were either set to 200 μL for the (male) mouse and rat liver and lung experiments or to 385.8 μL for the human liver lung. However, in the code provided as part of the 2010 report (IISRP-17520-1388) it appears that the later volume was used for all experiments with male tissues; i.e., from the 2004 paper

a) Please provide clarification on the sample volume(s) used for these various experiments. It makes sense that a single injection volume (~ 400 μL) was used for all experiments described in the 2004 paper, but that this was reduced to 200 μL in the subsequent analysis (female mouse and rat plus all kidney data).

b) Please provide information indicating the precision of the measurement sample sizes if other than one significant figure; i.e., if it was determined to be exactly 200.0 μL for data reported in Yang et al. (2012) but exactly 385.8 μL for data reported in Himmelstein et al. (2004).

3) Incubation vial volumes used in the Himmelstein et al. (2004) study

From the report for studies performed in 2010, IISRP-17520-1388, the vial volumes (weight of water required to fill the vials was ~ 11.65 or 11.63 g. However, in the model scripts provided the vial volume for the human tissue experiments was set to 0.0119573 L (11.9573 g).

In the code provided as part of the 2010 report (IISRP-17520-1388) it appears that the later volume was used for all experiments with male tissues; i.e., from the 2004 paper. This makes sense and lacking other information we will simply use 0.0120 L for all such samples.

If there are data to indicate the male mouse and rat studies conducted for the 2004 paper used vials that were 0.0116 L instead of 0.0120, please provide that information.

Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 9/5/2018 2:52:50 PM
To: HIMMELSTEIN, MATTHEW W [Matthew.W.Himmelstein@dupont.com]; Jerry Campbell [JCampbell@ramboll.com]
CC: Harvey Clewell [HClewell@ramboll.com]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]
Subject: RE: Chloroprene In Vitro model

Matt,

I'm working on a memo for you, but don't want to get overly nitpicky. This is from the report:

The total volume of Gerstel 10-mL vials used for the incubations was confirmed by gravimetric displacement with water. The measurement was made on 2 occasions once for the liver and lung microsome incubations (n=10 vials) and once for the kidney microsome incubations (n=10 vials). The respective mean (±SD) weights when filled completely with water at room temperature were 11.648 (±0.222) and 11.634 (±0.051) grams. These values were used directly (without correction for the specific gravity of water) to calculate the corresponding headspace volumes less the 1.0 mL used for the incubation liquid phase.

Now saying that these are the weights "when filled completely with water" indicates that it is the weight of the water ***and*** the vial. Reasonably you would have subtracted the weight of the empty vials, but that's not what it says here.

For the model parameters, this tells me that the measurement precision (or vial volume variance) is on the order of +/- 0.1 g. Hence the volume set in the model code should just be 11.6 mL, assuming that this was after taring.

-Paul

From: HIMMELSTEIN, MATTHEW W [mailto:Matthew.W.Himmelstein@dupont.com]
Sent: Wednesday, September 05, 2018 8:43 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

Sharing study report from which the manuscript was prepared. Microsomes for in vitro work were purchased or made in house at Haskell.

Matt

Matthew Himmelstein
DuPont Haskell Global Centers
Phone 302 451 4537

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Wednesday, September 05, 2018 8:16 AM
To: HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <JCampbell@ramboll.com>

Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: [EXTERNAL] RE: Chloroprene In Vitro model

Ah. I wasn't sure. The Yang paper says that animals were purchased from Charles River in Raleigh, so I was extrapolating.

-Paul

From: HIMMELSTEIN, MATTHEW W [mailto:Matthew.W.Himmelstein@dupont.com]
Sent: Tuesday, September 04, 2018 5:08 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

All in vitro incubations were conducted in my lab at Haskell.

Matt

Matthew Himmelstein
DuPont Haskell Global Centers
Phone 302 451 4537

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Tuesday, September 04, 2018 4:59 PM
To: HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: [EXTERNAL] RE: Chloroprene In Vitro model

Yes, certainly. I'll send something tomorrow.

I'm presuming that the kidney and female mouse/rat studies were all conducted at The Hamner, so just questions about the 2004 paper.

-Paul

From: HIMMELSTEIN, MATTHEW W [mailto:Matthew.W.Himmelstein@dupont.com]
Sent: Tuesday, September 04, 2018 4:52 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

Would it be possible to have a word document that categorizes and prioritizes your questions for me?

Matt

Matthew Himmelstein

DuPont Haskell Global Centers
Phone 302 451 4537

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Tuesday, September 04, 2018 4:26 PM
To: Jerry Campbell <JCampbell@ramboll.com>; HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: [EXTERNAL] RE: Chloroprene In Vitro model

I'm attaching the partial QA tables we (mostly Alan) have developed for the code. The good news is that other than the couple of start-up issues, the in vivo model code is clean, checks out. For the in vitro model we have the assumption of rapid equilibration still to be addressed. There are also a couple of parameter variations/possible discrepancies to be resolved:

VVIAL differs from default (0.01165 L) in the following files:
V_kidney.m (0.01163)
V_human.m (0.0119573)

This seems like it could just be differences in the specific vials/manufacturers, across time and labs, but the value for humans is overly precise, and why would the volume for vials for the kidney experiments be different from other experiments done by Yuching? And why would the volume for the human experiments conducted by Matt differ from other experiments in his lab? The impact is likely minimal, but in the absence of other documentation, either the default should be used for all experiments or only a Yang-vs-Himmelstein difference used.

As noted in the previous email, we also have that VINJ is set to 0.0003858 L for the human tissue incubations, but 0.0002 L otherwise. The value for humans seems overly precise. How was it determined and why wasn't it exactly 400 uL if other sampling was exactly 200 uL? That Matt changed the sample volume between his human in vitro experiments and rodent experiments needs to be confirmed (Matt, you can just say this in a reply email, if you recall doing that). Otherwise the volume should be consistent with the methods section of each paper: 400 uL for Matt's data, 200 uL for the Yang paper.

The changes/corrections of parameters for the in vivo model will need to be added to the QA table. There were a handful or so of small corrections on which we agreed and the fact that QCC for the mouse is set equal to QPC, which we accept as being consistent with other mouse in vivo data.

We will still need to evaluate the in vivo model against the in vivo PK data from Matt's in vivo paper, accepting that the nose-only chambers likely impacted (reduced) ventilation, but to assure that the model is otherwise consistent with those data. (Reduction in ventilation would not be assumed for open-chamber tox studies, but would be assumed to be independent of exposure concentration for the nose-only studies.) However, we won't attempt that until the in vitro equilibration issue is resolved.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Tuesday, September 04, 2018 12:15 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

I've attached the preliminary in vitro paper mentioned in the email.

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Tuesday, September 04, 2018 8:32 AM
To: HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Matt,

Can you send the 2001 paper, if it shows the rate of equilibration?

-Paul

From: HIMMELSTEIN, MATTHEW W [mailto:Matthew.W.Himmelstein@dupont.com]
Sent: Friday, August 31, 2018 7:37 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

Early in vitro work used a Buker shaker the kind of which we also had at CIIT, and was used for 1,3-butadiene in vitro metabolism as well as for all in vitro blood-to-air gas partitioning work pioneered by Gargas at the WPAFB.

We subsequently switched to a Gerstel head space/incubator/mixer auto sampler attached to the HP GC/MSD (see attached photo) http://www.gerstel.com/en/MPS-Agitator-Incubator-Stirrer.htm. All incubations were conducted with a ~1:10 liquid to air ratio (1 mL in 10 mL vial). My understanding is these facilitates rapid equilibration. Any preincubation time was conducted absent metabolizing protein or NADP. A lot of the initial methods were worked out and published in 2001. Sampling at 12 minute intervals was conducted but as I recall, the start times were staggered to fill in for a more continuous curve using multiple incubation vials.

Hope this helps.

I am out of the office today. Back Tuesday.

Matthew Himmelstein
DuPont Haskell Global Centers
Phone 302 451 4537

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Thursday, August 30, 2018 9:54 AM
To: Jerry Campbell <JCampbell@ramboll.com>; HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: [EXTERNAL] RE: Chloroprene In Vitro model

The other possible check is if experiments were run to check linearity of the initial slope with microsome concentration. I'm pretty sure that if mass transfer resistance is at play, you would see a less-than a doubling of the elimination rate when microsome concentration was doubled.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Thursday, August 30, 2018 9:41 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

There were control experiment data in the 2004 in vitro paper – Figure 3A.

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Thursday, August 30, 2018 9:39 AM
To: HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: FW: Chloroprene In Vitro model

Matt,

As a follow-up, see the email from Jerry below… You can follow the thread below that if you wish!

While the question Jerry asks is if you had gentle mixing going on, the information we really need is on the mass-transfer rate under those conditions. Did you ever run control experiments like the plot below, for another chemical if not CP?

Jerry: note that my incubations were also in a shaker, but I think the amount of surface motion would be dampened considerably in a smaller vial.

-Paul

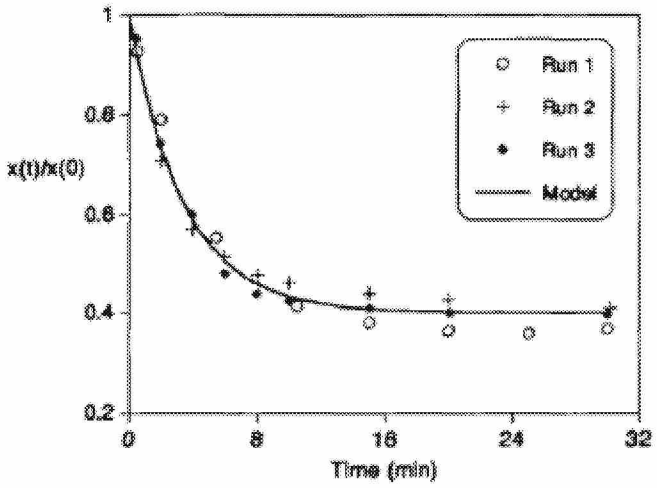

Fig. 3. Partitioning of benzene from liquid phase, into gas phase, in the absence of microsomes under incubation conditions (37°C shaker); $x(t)$ = concentration of benzene in the liquid phase at time = t; $x(0)$ = concentration of benzene in the liquid phase at time = 0. Different initial values, $x(0)$, were used for each run. The model is as depicted in Figure 1 with the rates of biotransformation ($r_1 - r_5$) set to zero.

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Thursday, August 30, 2018 9:10 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>
Subject: RE: Chloroprene In Vitro model

Paul,

Equilibration time question you might want to ask Matt is did they have a shaking sample heater for the headspace vials on their robot? I'm pretty sure they did. The version I had at UGA (was same system sold under another name) had controlled orbital shaking heater that could be set to very slow rotations per min (less than 10/min if I remember correctly) to provide gentle motion. It doesn't say explicitly in the method but it is possible that they used slow rotation to increase surface turnover and decrease liquid equilibration time. We generally used an orbital shaking water bath for non-volatile microsomal metabolism so I wouldn't be surprised if they did include some motion with their analysis too. .

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Wednesday, August 29, 2018 4:08 PM
To: Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>
Subject: RE: Chloroprene In Vitro model

P.S. If there are data for another chemical where the equilibration rate was measured, those could be used with an adjustment of the PC. But it has to be 100x or more faster than what I measured to give results that are indistinguishable from the model where it's assumed to be instantaneous, and that seems unlikely to me.

Or if not, but someone has the system running for other chemicals, it's only a handful of experiments, no tissues.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Wednesday, August 29, 2018 3:17 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>
Subject: RE: Chloroprene In Vitro model

In essence, there was only one sample scheme (every 0.2 hr or 12 min) but I think it may be more complicated than you have coded. It was an automated system – older version of the combi-pal autosampler. In the more highly sampled incubations (2004 paper in vitro paper), Matt reports that up to 5 vials were used to complete a time-course. So, while there was a mass of sample removed at each time, it wasn't linear throughout the whole run. He does state that samples were taken at 12 min intervals which coincides with the 1 vial system data in the female mouse and rat studies. The question is, can we assume that the 0.2 interval samples in the more highly sampled time-course is from a standardized staggered vial system:

Vial 1: 0, 0.2, 0.4, etc…
Vial 2: 0.05, 0.25, 0.45, etc…
Vial 3: 0.10, 0.30, 0.50, etc…
Vial 4: 0.15, 0.35, 0.55, etc…
Vial 5: ???

Jerry Campbell
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From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Wednesday, August 29, 2018 2:25 PM
To: Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: RE: Chloroprene In Vitro model

Jerry, Harvey,
Cc: Alan, Allen

So I've rigged the code and male mouse liver script to read the sample times from the data file and use those for the "injection" decrement. That should make it easy to apply to other experiments (species/tissues). It also has the separate air/medium compartments. "SET10" gives an initial concentration just in the air phase (I used it to check that the simulations fairly match my old BZ model when I try to simulate that).

I now have it plotting for both variable and fixed Km cases, though the fixed Km value was also hand-adjusted for only the male mouse liver data set. That was partly so I could create an acslX plot definition file (.aps, attached) for the comparison.

The revised .csl, male mouse liver .m file, and .aps are attached. Handling the outputs of multiple lengths is clunky, but as much as I'm willing to do right now.

So the issue as I see it is that one needs to know the mass transfer rate between the gas phase and medium in order to correctly interpret the in vitro data. I had assumed that Matt had done those experiments, included the transfer term, what we learned from working with James Bond. The rate will depend on the surface area in the vial and rate of shaking

in the incubator. The rate that I got is clearly too slow to be consistent with the data, but that doesn't mean it's not partially rate-limiting in these experiments. And I don't have a strong intuition for how much it might matter. But the impact will be largest when the rate of metabolism is highest.

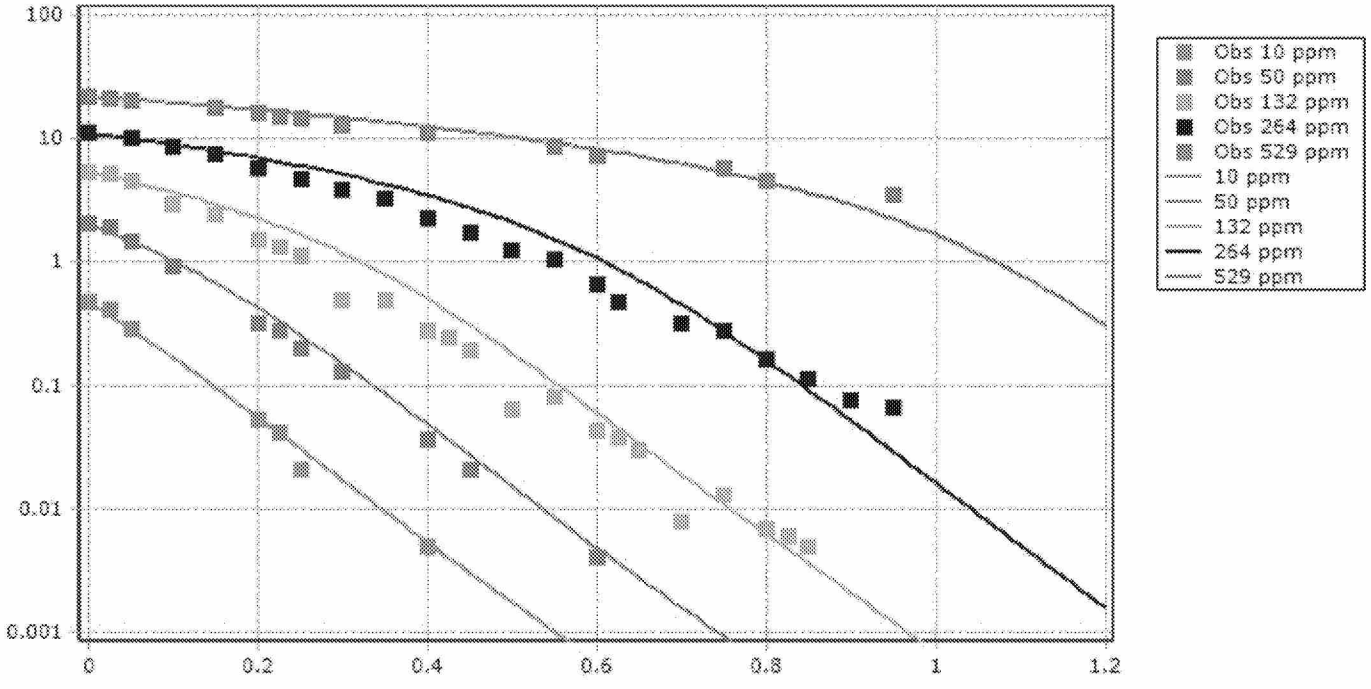
On the other hand, under-counting the sampling (male liver and lung data from Matt) will result in an over-estimate of metabolic rate for those experiments. That will have the largest relative impact when metabolism is slow. At least that just requires an adjustment of the code.

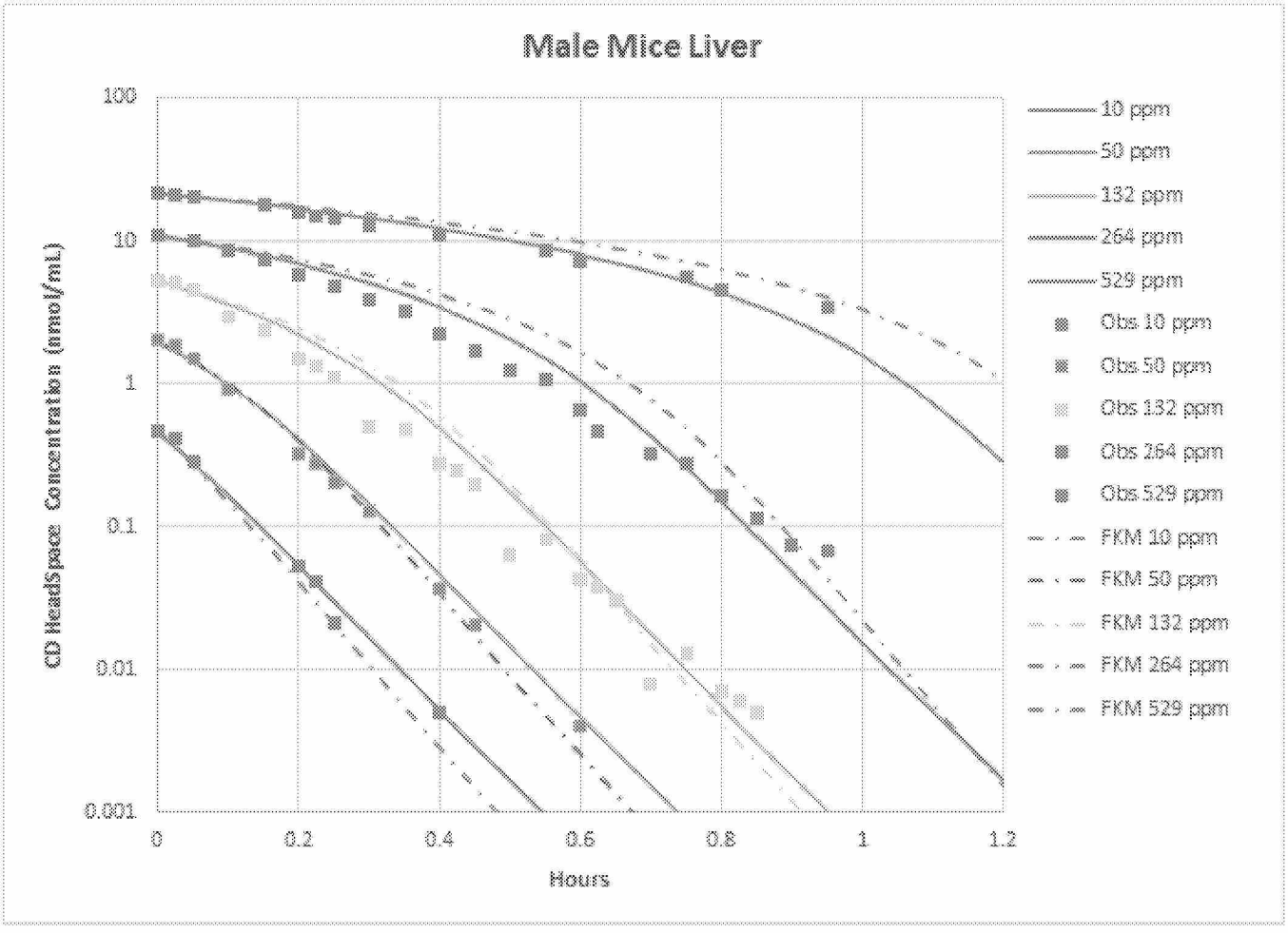
With regards,
-Paul

From: Schlosser, Paul
Sent: Tuesday, August 28, 2018 4:50 PM
To: 'Jerry Campbell' <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

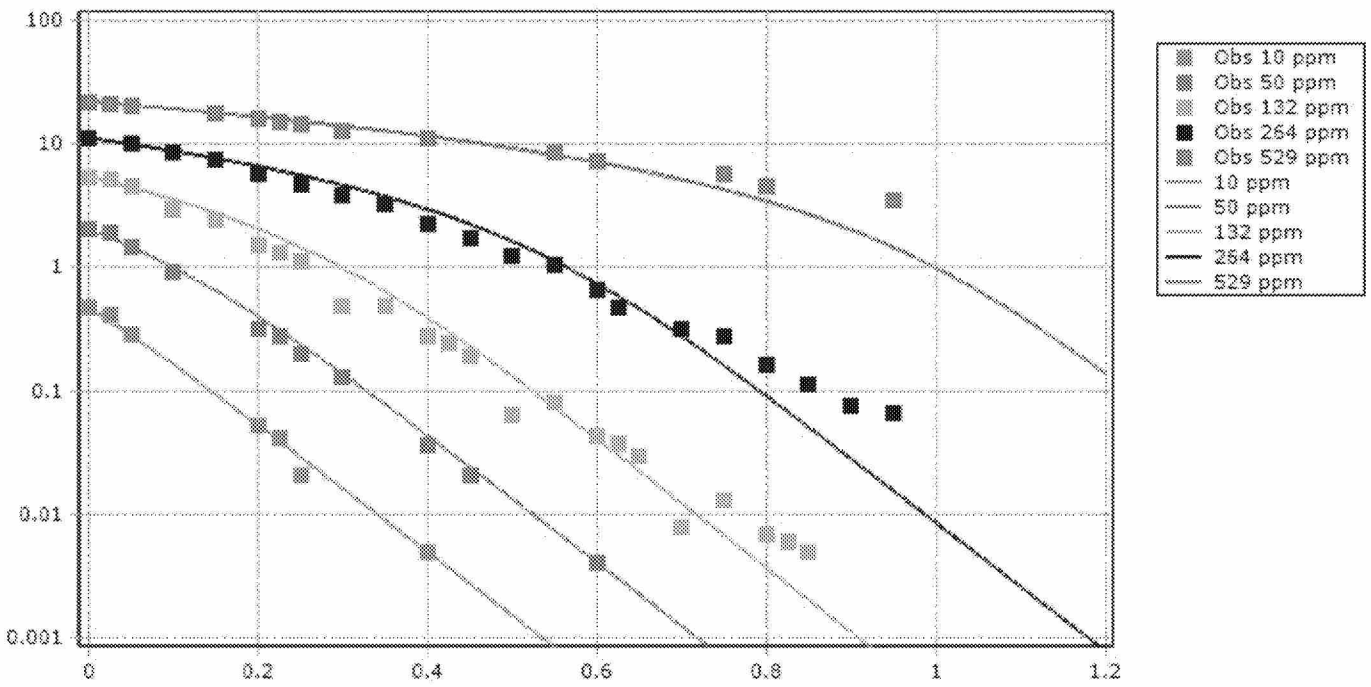
OK, so the first other thing I noticed was that the sampling time (TI) was set to 0.2 h, but clearly samples were taken at a higher frequency. To somewhat quickly get the model to allow for a variation in that, I can't use the procedural, as different sampling intervals changes the length of the output vector, so I can't combine the results in a single array. There's other ways around that, but my cluge was to treat sampling as a continuous loss at rate = VING/TI, where TI is calculated for each data set as TFINAL/NSAMPLE; i.e., the time of the final sample over the number of samples minus the one at time 0.

With the model changed to allow distribution between air and medium (so separate sub-compartments), TI fixed at 0.2 h, but an extremely high mass transfer coefficient (KGL) for air-medium, I get this, compared to the plot (for the Yang parameters) in the spreadsheet that Jerry sent (keep scrolling down):





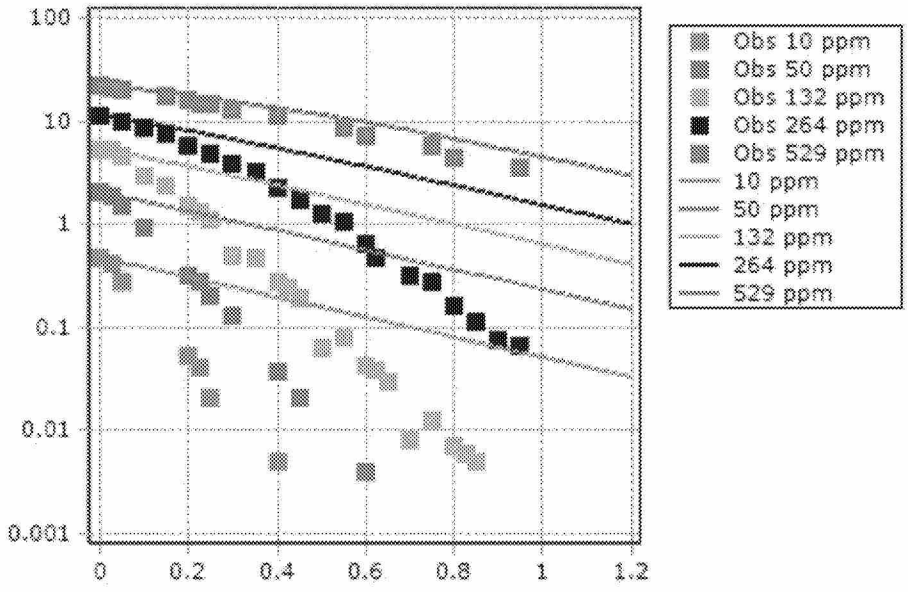
I'd say that's pretty good reproduction! Now, using the variable sampling time (TI), as described above:



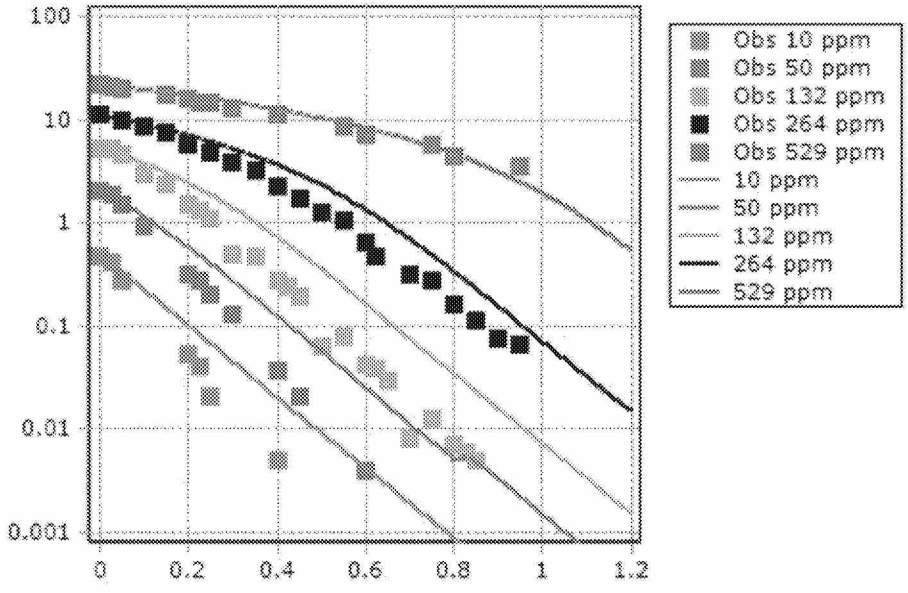
The difference isn't huge, but it's a difference…. For many of the experiments the interval is a fixed 0.2 h, but the male rat and mouse lung, and male rat lung are much more frequent. For the male mouse lung the metabolism is slower, which means the relative impact of this term will be greater.

Ideally the actual sample times should be used, with the scheduled procedural. That's a bit more programming but not terribly difficult. One will just need to deal with the fact that the output from each simulation will be a vector of a different length.

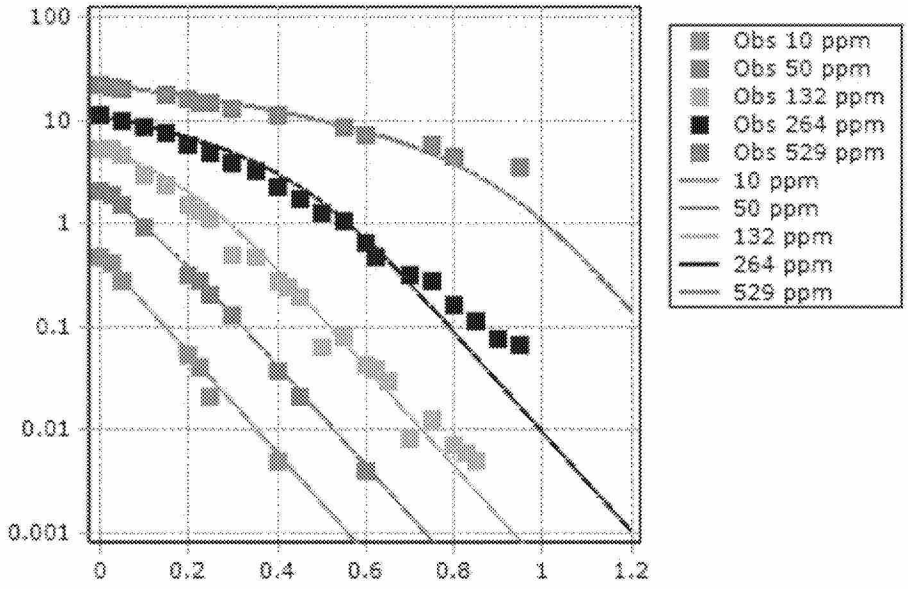
The bigger thing is the gas phase mass transfer. From my '93 benzene paper, the kg = 0.434 ml/min * 60 min/h * 0.001 L/ml = 0.026 L/h. Using that constant, so rate of movement from air to liquid (net) = 0.026*(Ca1 – Cm1/P1), I get:



Really bad, but then there may have been much less mixing in my smaller vials than Matt's, so I increased KGL by 10x, to 0.26:



I then reduced the Km from 1.36 to 0.8 (a bit of trial and error):



Based on this, I'd say that there's a very good chance that the gas-liquid mass transfer is a significant factor, and is likely to impact the estimation of Km (perhaps the goodness of fit of the fixed-Km model). The difficulty is that we need control incubation data to determine the correct value of KGL.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Tuesday, August 28, 2018 11:07 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Yes, it should be +ARLOSS. I must have hit the wrong key yesterday when I noticed it was missing from the equation.

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From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Tuesday, August 28, 2018 8:42 AM
To: Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Thanks, Jerry. I've forwarded to Alan who is getting back to his evaluation of the primary model. I'm hoping we can get through the model code evaluation by the end of next week…

Well, I just looked at the .csl and see this:

```
!MASS BALANCE
  CHECK1 = A10 - (A1+A1M+A1I+ ARLUNGVK-ARLOSS)
```

But that should be +ARLOSS?

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Monday, August 27, 2018 4:30 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>
Subject: Chloroprene In Vitro model

Paul,

I've uploaded a zip folder (INVITROMODEL AND GRAPHS.zip) with the full workspace for the in vitro model and Excel files with the figures. There is a spreadsheet with a list of the m-files and a short description. Let us know if something doesn't work or you have any questions.

Jerry Campbell

Managing Consultant

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Francais Deutsch Italiano Espanol Portugues Japanese Chinese Korean

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Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 8/10/2018 3:48:43 PM
To: Jerry Campbell [JCampbell@ramboll.com]
CC: Harvey Clewell [HClewell@ramboll.com]; Allison Franzen [AFranzen@ramboll.com]; cvanlandingham@ramboll.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usereda39e51]; Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]; Kapraun, Dustin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3a53c151b92a472fbfb295ed5df982a7-Kapraun, Du]
Subject: RE: transmission of PBPK model for chloroprene
Attachments: 1st_Trimester_BBDR_R_MCSim20170822.zipped

So Dustin set it up in for the sequence of bolus doses in the Greer study for perchlorate using the 'events' input structure. My understanding is that this effectively stops the ode solver at each event, implements the change specified for that event, then re-starts the solver. If you have a parameter that multiplies inhalation concentration that switches 0-1 for off-on, call it inhon, then, then you could have the set of 'on' events and 'off' events which flip it back and forth.

We'd also run each exposure level separately.

See the greer_test.r script in the attached.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Friday, August 10, 2018 10:14 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; cvanlandingham@ramboll.com; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>
Subject: RE: transmission of PBPK model for chloroprene

Paul,

There are quite a few ways in R to input exposure. Most seem a little more cumbersome than acslX but only if you were familiar with the schedule statement in acslX. I have some complex inputs that I actually had to create as csv files and read them in to the simulation which is why I started using a forcing function. You will need more than a few points to run the in vivo simulation. Otherwise, you only need the last value for the average amount metabolized metrics.

I'm not sure what you mean by stopping the simulation. Do you mean setting up every concentration as a separate .in file and then calling them sequentially in R or is there a way to run multiple MCSim inputs directly in a single R script without the .in file? MCsim doesn't allow control of the output matrix name unless you using the Monte Carlo input so I've generally avoided running directly in MCSim unless necessary? Do you have simple example you could share for your schedule setup? It might be an easier way to run these sims since the inputs are relatively defined.

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From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Friday, August 10, 2018 8:31 AM
To: Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>
Subject: RE: transmission of PBPK model for chloroprene

Jerry, others,
Cc: Alan, Dustin

And thanks! Alan Sasso had already gotten most of the way there (identified it as a scheduling issue). So these may provide a good template.... We've been working in the MCSim language, and have some equivalents to the acslX scheduling, but less convenient.

I looked at the actual 'signal' array. Do you really need to set the time-points that closely? Maybe our approach of just stopping the simulation, reset the parameter, starting again isn't so bad!

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Thursday, August 09, 2018 5:47 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; cvanlandingham@ramboll.com
Subject: RE: transmission of PBPK model for chloroprene

Paul,

Replace the animal scripts with these. Someone, who shall remain nameless, decided to change the simulation to 2 weeks of exposure but set the file to only expose for the first week (dexpend = 5 instead of 12). That's why you get a dose metric that is exactly ½ the table value.

I can walk you through the forcing function and how it works. I had set it up to be similar to the "schedule" format that was traditionally used in acslX where one would set exposure length and number of days per week to expose. It may be adding complication that is unnecessary for this model where we could switch use events. You can plot the forcing function after running a simulation. The matrix is named signal and there is only one import for this model.

plot(signal$ftime,signal$import1, 'l')

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Managing Consultant

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From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Thursday, August 09, 2018 4:29 PM
To: Jerry Campbell <JCampbell@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Kicking the tires...

I tested a couple of dose metric scripts. The mouse and rat ones I checked seem to produce values ('rout') almost exactly 50% of what's in the 'dose metrics' tab. But the human dose metric script matched.

```
> source('C:/Users/pschloss/Downloads/Desktop/chloroprene_fin/Human_dose_metric_2.R')
> rout
   ppm       AMP       AMPLU AMPK
1 12.3 0.2530232 0.04041056    0
2 32.0 0.6581998 0.10513844    0
3 80.0 1.6450145 0.26288161    0
> source('C:/Users/pschloss/Downloads/Desktop/chloroprene_fin/Male_rat_dose_metric_2.R')
> rout
   ppm       AMP      AMPLU       AMPK
1 12.3 0.4482158 0.1075722 0.06755752
2 32.0 1.1740539 0.2822177 0.09051064
3 80.0 2.9397783 0.7104413 0.10875550
```

There are no scripts to produce the plots sent by email (via Harvey) on 7/31. We will need them. It would be good to have plots for the kidney data/fits too, though it's a fairly small contributor.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Monday, August 06, 2018 9:30 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; cvanlandingham@ramboll.com; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

I was just getting to that option. See if this will work.

Jerry Campbell
Managing Consultant

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jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 9:26 AM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Try just changing the file-extension from .zip to .txt and sending as an attachment. I'm trying to unzip the thing from the sharepoint site and just getting a spinning wheel.

From: Cynthia Van Landingham [mailto:cvanlandingham@ramboll.com]
Sent: Monday, August 06, 2018 9:19 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell

<JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Unfortunately, I believe that the restrictions are on your end not ours. We can all see the files no problem.

Cynthia

Cynthia Van Landingham
Senior Managing Consultant

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cvanlandingham@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 8:18 AM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

I tried to just download it. Does it have to be this complicated? We'll be sharing with everyone as part of our open and transparent process…

-Paul

From: Cynthia Van Landingham [mailto:cvanlandingham@ramboll.com]
Sent: Monday, August 06, 2018 9:13 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Paul,
Did you download the zip file to your hard drive and then open or did you open it on the OneDrive site? If you did not try this, selecting all the files and allowing OneDrive to produce one download zip may be best. The chloroprene_model.o_error.txt file is not in the zip we created so may be something that is being created due to the download process. Please read that file to find out if your IT security set-up is preventing files from being extracted.

Thanks, Cynthia

Cynthia Van Landingham
Senior Managing Consultant

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cvanlandingham@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 7:53 AM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon

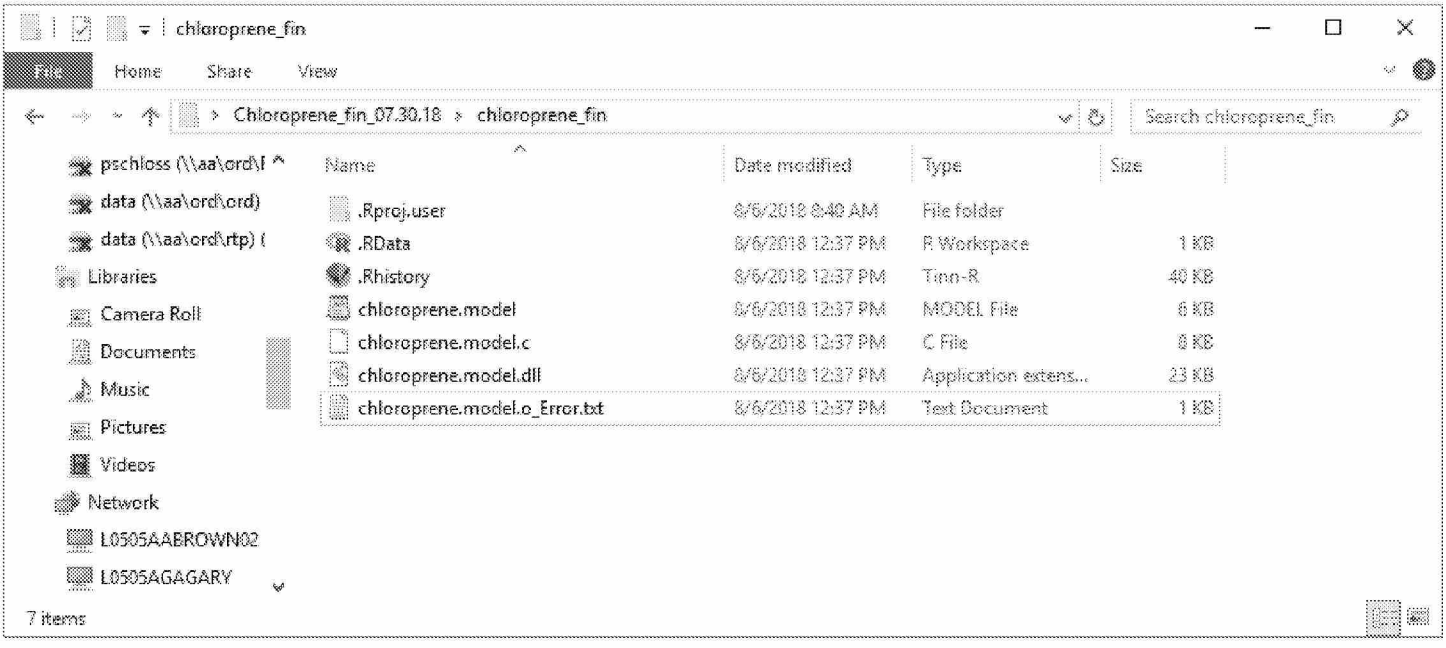
<myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Harvey,

I sent a separate email to Alison. Below is a screenshot of the model folder that I got. There are none of the scripts listed in the Excel 'documentation' file.

Once we have those, give us some time to look at it. Hopefully it's easy enough to figure out, but we can let you and Jerry know if we need a walk-through.

-Paul



From: Harvey Clewell [mailto:HClewell@ramboll.com]
Sent: Friday, August 03, 2018 2:02 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Robinan Gentry <rgentry@ramboll.com>; cvanlandingham@ramboll.com; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: transmission of PBPK model for chloroprene

Hi Paul

As promised, we are providing you with the PBPK model for chloroprene written in R, with all the associated scripts and documentation. You should have received a separate email with an invitation to access the files on Microsoft OneDrive. Please let me if you have any problem downloading or opening them. Jerry Campbell would be happy to come over to EPA to help you set up the run environment in R studio and answer any questions you may have about running the model.

I'm looking forward to talking with you about the model and discussing any questions, suggestions, or concerns regarding it. Would it be possible to arrange an initial meeting sometime in the next few weeks. Miyoung Yoon is completing her review of the metabolism parameter scaling approach and I would like to be able to include you in the discussion of her recommendations.

Harvey Clewell

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```
#--------------------------------------------------------------------------------
# baseline_pregnancy.R
#
# Translated from "baseline pregnancy.m".
# Author: Paul Schlosser, U.S. EPA, February-August 2017
# Translator: Dustin Kapraun, U.S. EPA, July-August 2017
#
# This script runs middle, low, and high simulations for model verification vs.
# pregnancy data, shown in Figures 57-59 of the Appendix. Plots are created in
# "pregplots.xls". This script writes numerical results to several CSV files
# identified below. The CSV files must be opened and the results copied to the
# appropriate tabs/cells in the XLS file.
#
# Note that the calibration script "non_pregnant_ss_set.R" is called with
# PDOSEUG_I = 90 ug/d, as explained in the Appendix section "Thyroid hormone
# levels and iodine intake in non-pregnant women", but then iodine intake
# levels are set from the 'idose' level for each thyroid parameter set below.
#--------------------------------------------------------------------------------

# Run the script "BBDRPreg_params.R", which assigns values to some variables,
# sets values for parameters in the "parms" vec, and sets initial conditions
# for state variables based on a non-pregnancy simulation to steady state.
source("BBDRPreg_params.R")

# Simulation details for final (post-calibration) simulations.
GSTART_f = 3000
TSTOP_f = GSTART_f + 16 * 24 * 7        # Through 16 weeks of pregnancy.
CINT_f = 12
times_f = seq(from=0, to=TSTOP_f, by=CINT_f)
ga_f = (times_f - GSTART_f) / (7 * 24)  # Simulation time in gestational weeks.

# We will save results for simulation times starting from about 2 weeks before
# the beginning of pregnancy.
num_times = sum(ga_f >= -2.05)
sim_end_idx = length(times_f)
ga_start_idx = sim_end_idx - num_times + 1

# Identifiers for thyroid parameter sets from Table 7 of the Perchlorate BBDR
# Appendix.
v_vec = c(1, 2, 3)

# Ratio of NHANES median (50th percentile) for PTSHV to 2.5th, 50th, and
# 97.5th percentiles.
pt_vec = 1.39 / c(0.45, 1.39, 3.49)

# One simulation will be run for each thyroid parameter set (v_val) and each
# PTSHV ratio (pt_val). Thus, the total number of simulations is...
num_sims = length(v_vec) * length(pt_vec)
```

```
# Allocate space to save results for T4, fT4, TSH, T3, and fT3.
T4_save = matrix(data=NA, nrow=num_times, ncol=num_sims)
fT4_save = matrix(data=NA, nrow=num_times, ncol=num_sims)
TSH_save = matrix(data=NA, nrow=num_times, ncol=num_sims)
T3_save = matrix(data=NA, nrow=num_times, ncol=num_sims)
fT3_save = matrix(data=NA, nrow=num_times, ncol=num_sims)

# Set the current column to which simulation results will be written.
curr_col = 1

# Obtain initial values for iodide state variables.
source("BBDRPreg_params.R")

# Run a simulation for each combination of v_val and pt_val values.
for (v_val in v_vec) {
    if (v_val == 1) {
        idose = 170.2
        BT4 = 0.01845
        AOBT4 = -0.07782
        CT4TAR = median(c(111.8, 112.4, 100.3))
        CT3tar = median(c(1.89, 1.89, 1.74))
        FRT40 = median(c(1.32e-4, 1.40e-4, 1.03e-4))
        FRT30 = median(c(2.77e-3, 2.61e-3, 2.77e-3))
        TSHTAR = median(c(1.37, 2.04, 1.39))
        ABNDMAX0 = 17e6
        Abound_i = 15e6 / MWI
    }
    else if (v_val == 2) {
        idose = 38
        BT4 = 0.01351
        AOBT4 = -0.1013
        CT4TAR = min(c(66.9, 81.0, 79.8))
        CT3tar = min(c(1.36, 1.49, 1.26))
        FRT40 = median(c(1.60e-4, 1.54e-4, 0.97e-4))
        FRT30 = median(c(2.92e-3, 2.74e-3, 3.17e-4))
        TSHTAR = max(c(4.09, 5.03, 3.49))
        ABNDMAX0 = 15e6
        Abound_i = 13e6 / MWI
    }
    else if (v_val == 3) {
        idose = 763.4
        BT4 = 0.02845
        AOBT4 = - 0.06221
        CT4TAR = max(c(165.9, 149.0, 142.4))
        CT3tar = max(c(3.05, 2.43, 2.55))
        FRT40 = median(c(1.07e-4, 1.31e-4, 0.97e-4))
        FRT30 = median(c(2.20e-3, 2.48e-3, 2.36e-3))
```

```
        TSHTAR = min(c(0.41, 0.78, 0.45))
        ABNDMAX0 = 19e6
        Abound_i = 17e6 / MWI
    }

    # Update the model parameters for which values were provided above.
    parms["bT4"] = BT4
    parms["AobT4"] = AOBT4
    parms["CT4TAR"] = CT4TAR
    parms["FRT40"] = FRT40
    parms["FRT30"] = FRT30
    parms["TSHTAR"] = TSHTAR
    parms["Abndmax0"] = ABNDMAX0
    # NOTE: Abound_i and CT3tar are used in "non_pregnant_ss_set.R".

    # Calibrate for 90 ug/d.
    parms["Pdoseug_i"] = 90.0
    source("non_pregnant_ss_set.R")

    # Set iodide dosing rate and timing parameters for final (post-calibration)
    # simulations.
    parms["Pdoseug_i"] = idose
    times = times_f
    for (pt_val in pt_vec) {
        # Set conditions for final (pregnancy) simulation.
        parms["GSTART"] = GSTART_f

        # Set parameters related to TSH regulation.
        parms["pTSHv"] = pt_val
        parms["pTSHk"] = pt_val
        parms = initParms(parms)

        # Run simulation.
        out = ode(Y0, times, func="derivs", parms=parms, dllname=dll_name,
                  initfunc="initmod", nout=length(Outputs), outnames=Outputs)

        # Save results.
        T4_save[ , curr_col] = out[ga_start_idx:sim_end_idx, "CT4"]
        fT4_save[ , curr_col] = 1000 * out[ga_start_idx:sim_end_idx, "CfT4"]
        TSH_save[ , curr_col] = out[ga_start_idx:sim_end_idx, "TSH"]
        T3_save[ , curr_col] = out[ga_start_idx:sim_end_idx, "CT3"]
        fT3_save[ , curr_col] = 1000 * out[ga_start_idx:sim_end_idx, "CfT3"]
        curr_col = curr_col + 1
    }
}
# Add a column for the simulation times.
T4_save = cbind(ga_f[ga_start_idx:sim_end_idx], T4_save)
fT4_save = cbind(ga_f[ga_start_idx:sim_end_idx], fT4_save)
```

```
TSH_save = cbind(ga_f[ga_start_idx:sim_end_idx], TSH_save)
T3_save = cbind(ga_f[ga_start_idx:sim_end_idx], T3_save)
fT3_save = cbind(ga_f[ga_start_idx:sim_end_idx], fT3_save)

# Save results to CSV files. "t4sv.csv" contains results for T4
# concentrations, etc.
write.table(T4_save, "t4sv.csv", sep=",", row.names=F, col.names=F)
write.table(fT4_save, "ft4sv.csv", sep=",", row.names=F, col.names=F)
write.table(TSH_save, "tshsv.csv", sep=",", row.names=F, col.names=F)
write.table(T3_save, "t3sv.csv", sep=",", row.names=F, col.names=F)
write.table(fT3_save, "ft3sv.csv", sep=",", row.names=F, col.names=F)
```

```
#--------------------------------------------------------------------------
# bbdr.model
#
# A biologically-based dose response model for perchlorate, iodide, and thyroid
# hormones in a human adult female prior to conception and during the first
# trimester of pregnancy.
#
# The model was translated from the ACSLX model specification language (".csl")
# to the MCSim model specification language (".model") in July-August 2017 by
# Dustin Kapraun (U.S. EPA).
#
# This model was created in February-August 2017 by Paul Schlosser (U.S. EPA)
# in consultation with Jeff Fisher (U.S. FDA), Teresa Leavens (PK Consultant),
# and Dustin Kapraun (U.S. EPA). It is based upon a BBDR model for a lactating
# mother that was developed by Jeff Fisher (U.S. FDA), Annie Lumen (U.S. FDA),
# Eva McLanahan (U.S. EPA, currently CDC), Paul Schlosser (U.S. EPA), and
# Teresa Leavens (PK Consultant).
#
# This model describes maternal iodide, thyroid hormone, and perchlorate
# kinetics and dynamics prior to and up through the first trimester of
# pregnancy.  A variable pre-pregnancy simulation time (GSTART) allows the
# system to reach steady state prior to pregnancy.  The model does not include
# explicit fetal or placental compartments because it is focused on maternal
# predictions. The fetus and placenta mass and blood flow are included in the
# "rest-of-body" tissue group.
#
# Specific changes are noted in comments with initials "PMS" for Paul Schlosser.
#
# *** Except where otherwise noted, derivation/calibration of parameter values
# is explained in the companion document, 1T Model Parameters.07-27-17.docx,
# which in turn cites specific Excel spreadsheets and data files used, with
# citations.
#
# Note that many of the default parameter values below are over-ridden by
# values in "BBDRpreg_params.R", "non_pregnant_ss_set.R", or other specific
# ".R" scripts.
#
# Primary model units are nmol, L, h; however, units for input parameters vary
# as indicated in comments.
#
# Specific changes and comments during translation from ACSLX to MCSim are
# indicated by initials "DFK" for Dustin Kapraun.
#--------------------------------------------------------------------------


#--------------------------------------------------------------------------
# STATE VARIABLES for the model (for which ODEs are provided).
```

```
States = { Adose_i,          # Amount of iodide dosed (total) (nmol).
           Adose_ri,         # ... radioiodide dosed (total) (nmol).
           Astom_ri,         # ... radioiodide in the stomach (nmol). This state
                             #     variable was added to allow for radioiodide
                             #     bolus dosing. -- DFK 8-2-2017
           Aplasma_i,        # ... iodide in plasma (nmol).
           Aplasma_ri,       # ... radioiodide in plasma (nmol).
           Aelim_i,          # ... iodide eliminated (total) (nmol).
           Aelim_ri,         # ... radioiodide eliminated (total) (nmol).
           Arob_i,           # ... iodide in the rest-of-body (nmol).
           Arob_ri,          # ... radioiodide in the rest-of-body (nmol).
           AthyB_i,          # ... iodide in the thyroid blood (nmol).
           AthyB_ri,         # ... radioiodide in the thyroid blood (nmol).
           Aupthy_ri,        # ... radioiodide transported into thyroid (total)
                             #     (nmol).
           Abound_i,         # ... iodide bound in thyroid tissue (nmol).
           Abound_ri,        # ... radioiodide bound in thyroid tissue (nmol).
           AelimT4,          # ... T4 eliminated (total) (nmol).
           AelimrT4,         # ... radio-T4 eliminated (total) (nmol).
           AT4,              # ... T4 in the volume of distribution (nmol).
           ArT4,             # ... radio-T4 in the volume of distribution (nmol).
           AelimT3,          # ... T3 eliminated (total) (nmol).
           AelimrT3,         # ... radio-T3 eliminated (total) (nmol).
           AT3,              # ... T3 in the volume of distribution (nmol).
           ArT3,             # ... radio-T3 in the volume of distribution (nmol).
           AIoral_p,         # ... perchlorate ingested orally (nmol).
           Astom_p,          # ... perchlorate in the stomach (nmol).
           Aplasma_p,        # ... perchlorate in the plasma (nmol).
           Aelim_p,          # ... perchlorate eliminated (nmol).
           Abind_p,          # ... perchlorate bound in the plasma (nmol).
           ARBC_p,           # ... perchlorate in red blood cells (nmol).
           Arob_p,           # ... perchlorate in the rest-of-body (nmol).
           AthyB_p,          # ... perchlorate in the thyroid blood (nmol).
           AthyT_p           # ... perchlorate in the thyroid tissue (nmol).
};
# End of STATE VARIABLES.
#-------------------------------------------------------------------------------


#-------------------------------------------------------------------------------
# OUTPUT VARIABLES for the model (which can be obtained at any point in time
# as analytic functions of state variables, inputs, and parameters).

Outputs = { GA,              # Gestational age (weeks).
            BW,              # Body mass (kg).
            Ca_i,            # Concentration of iodide in plasma (nmol/L).
            Crob_i,          # ... in rest-of-body (nmol/L).
            Cvrob_i,         # ... in veins leaving rest-of-body (nmol/L).
```

```
CthyB_i,         # ... in thyroid blood (nmol/L).
Cvtotal_i,       # ... in veins (average) (nmol/L).
CthyT_fi,        # ... free (unbound) in thyroid tissue (nmol/L).
Cthy_i,          # ... in the whole thyroid (average) (nmol/L).
Athy_i,          # Total amount of iodide in the thyroid (nmol).
Ca_ri,           # Concentration of radioiodide in plasma (nmol/L).
Crob_ri,         # ... in rest-of-body.
Cvrob_ri,        # ... in veins leaving rest-of-body.
CthyB_ri,        # ... in thyroid blood.
Cvtotal_ri,      # ... in veins (average) (nmol/L).
CthyT_fri,       # ... free (unbound) in thyroid tissue (nmol/L).
Cthy_ri,         # ... in the whole thyroid (average) (nmol/L).
Athy_ri,         # Total amount of radioiodide in the thyroid (nmol).
CT4,             # Concentration of T4 (nmol/L).
CfT4,            # Concentration of free T4 (nmol/L).
CrT4,            # Concentration of radio-T4 (nmol/L).
CT3,             # Concentration of T3 (nmol/L).
CfT3,            # Concentration of free T3 (nmol/L).
CrT3,            # Concentration of radio-T3 (nmol/L).
Ca_p,            # Concentration of perchlorate in plasma (nmol/L).
CAbind_p,        # ... in plasma proteins (bound) (nmol/L).
CAtot_p,         # ... in plasma and plasma proteins (nmol/L).
CRBC_p,          # ... in red blood cells (nmol/L).
Crob_p,          # ... in rest-of-body (nmol/L).
Cvrob_p,         # ... in veins leaving rest-of-body (nmol/L).
CthyB_p,         # ... in thyroid blood (nmol/L).
CthyT_p,         # ... in thyroid tissue (nmol/L).
Cthy_p,          # ... in the whole thyroid (average) (nmol/L).
Cvtotal_p,       # ... in veins (average) (nmol/L).
VDT4,            # Volume of distribution for T4 (L).
VDT3,            # Volume of distribution for T3 (L).
Vpls,            # Volume of plasma (L).
VthyB,           # Volume of thyroid blood (L).
VthyT,           # Volume of thyroid tissue (L).
Vrob,            # Volume of rest-of-body (L).
CLuI,            # Urinary clearance of iodide (L/h).
PAthy_i,         # Permeability value for iodide in thyroid (L/h).
TSH,             # Concentration of TSH (mIU/L).
hCG,             # Concentration of hCG (kIU/L).
VmaxNIS_thy_i,   # Maximum rate of NIS transport of iodide (nmol/h).
Aboundmax,       # Maximum capacity for organified iodide in thyroid
                 #  tissue (nmol).
Qthy,            # Blood flow rate to thyroid (L/h).
Qbal,            # Blood flow balance. (Should be zero.)
Vbal,            # Volume balance. (Should be 100%.)
Mbal_i,          # Iodide mass balance. (Should be constant.)
Mbal_p,          # Perchlorate mass balance. (Should be constant.)
```

```
            CLuI
};
# End of OUTPUT VARIABLES.
#-------------------------------------------------------------------------------


#-------------------------------------------------------------------------------
# INPUT VARIABLES for the model (which are independent of other variables, and
# which may vary in time).
Inputs = {};

# End of INPUT VARIABLES.
#-------------------------------------------------------------------------------


#-------------------------------------------------------------------------------
# PARAMETERS for the model (which are independent of time).

# Experimental parameters.
GSTART = 70000.0;       # Time of conception (h).
BW0 = 70.0;             # Maternal body mass (kg) prior to conception.

VFpls = 0.0359;         # Proportion of body volume (or mass, BW) that is
                        #  plasma.
Hct0 = 0.394;           # Proportion of total blood volume that is red blood
                        #  cells prior to pregnancy.
VFthy = 1.34e-4;        # ... thyroid.
VFthyB = 0.276;         # ... thyroid blood (proportion of VFthy).
VFthyT = 0.724;         # ... thyroid tissue (proportion of VFthy).
VDFT40 = 0.162;         # ... initial/non-pregnant volume of distribution for
                        #     T4.
VDFT30 = 0.603;         # ... initial/non-pregnant volume of distribution for
                        #     T3.
                        # VDT4 and VDT3 are assumed to scale with total BW but
                        #  proportion of total BW decreases during pregnancy.

# Fractional blood flows. Non-pregnant blood flows scale as BW^0.75. A
# function for an absolute change with gestational age (GA), independent of
# body mass (BW), is applied for total cardiac output (QC) during pregnancy.
# Flow to thyroid (Qthy) is assumed to increase in proportion to volume of
# thyroid (Vthy) during pregnancy. Vthy is assumed to increase in proportion
# to total BW.
QFC0 = 13.378;          # Initial/non-pregnant cardiac output coefficient
                        #  (L/hr/kg^0.75).
QCG = 141.4;            # Multiplier (L/h) for increase in QC with gestation.
QFthy0 = 0.015;         # Initial proportion of blood flow to the thyroid
                        #  (Leggett & Williams, 1995).
```

```
# Molecular weights (g/mol).
MWI = 126.9;            # Iodide.
MWT4 = 776.87;          # T4.
MWT3 = 650.98;          # T3.
MWClO4 = 99.45;         # Perchlorate.

# Partition coefficients (no units).
Prob_i = 0.243;         # Iodide partitioning into rest-of-body (ROB).
Pthy_i = 0.15;          # Iodide partioning into thyroid.
Prob_p = 0.558;         # Perchlorate partitioning into ROB.
PRBC_p = 0.8;           # Perchlorate partioning into red blood cells (RBCs)
                        #  (Clewell et al., 2007).
Pthy_p = 0.13;          # Perchlorate partitioning into the thyroid.


PARBCc_p = 10.0;        # Diffusion between RBCs & plasma (L/hr/kg^0.75)
KunbC_p = 0.03;         # Rate constant for release of protein-bound perchlorate
                        #  to plasma (L/hr/kg^0.75).

# Kinetic parameters for iodide.
VmaxNISF_thy_i = 3800;  # Vmax of NIS in thyroid (nmol/hr/kg^0.75).
KmNIS_i = 3.15e4;       # Km of NIS in thyroid (nmol/L).

# Kinetic parameters for perchlorate.
VmaxNISF_thy_p = 650;   # Vmax of NIS in thyroid (nmol/hr/kg^0.75).
KmNIS_p = 603.32;       # Km of NIS in thyroid (nmol/L) (=6e4/MWClO4).
VmaxC_Bp = 5.9;         # Vmax for M-M binding in serum (nmol/hr/kg^0.75).
Km_Bp = 181;            # Km for M-M binding in serum (nmol/L). -- PMS 4-22-15

# Rate constants.
Abndmax0 = 17.0e6;      # Max amount of organified iodide in pre-pregnancy (ng)
Kbind_i= 0.2232;       # 2nd order organification rate (1/nmol/hr). Value is
                        #  replaced by running "non_pregnant_ss_set.R", but
                        #  derivation of nominal value is provided below.
                        #
                        # Rbind_i = AthyT_fi*Aremain*Kbind_i.  For the target
                        #  euthyroid state (to match CT4tar and CT3tar), with
                        #  iodine intake of 177 ug/d, Cbi and the net rate of
                        #  uptake need to be 15.9 nM and 46.43 nmol/h,
                        #  respectively.  If it's assumed that at that point
                        #  the remaining binding capacity Aremain_I =
                        #  Cboundmax*VthyT/16 = 7874.4 nmol and the free iodine
                        #  concentration in the thyroid (Cfi here) is at
                        #  equilibrium with the blood, then Cfi = 2.38 nM. In
                        #  order to then have Rbind_i equal the uptake,
                        #  46.43 nmol/h = (2.38 nM*0.0111 L)*(7874.4 nmol)
                        #  *Kbind_i, so: Kbind_i = (46.43 nmol/h)/(2.338*0.0111
                        #  *7874.4 nmol^2) = 0.2232.
```

```
                        #
KprodT4F = 2.45e-6;     # First order T4 production rate (1/hr/kg^0.75).
KprodT3F = 7.62e-7;     # First order T3 production rate (1/hr/kg^0.75).
                        # Note that KprodT4 and KprodT3 are proportional to
                        #  BW0^0.75 during pre-pregnancy, and due to
                        #  regulation, are independent of BW during pregnancy.

KdegT3F = 1.63e-3;      # First order serum T3 degradation rate (1/hr/kg^0.75).
KdegT4F= 1.9e-4;       # First order Serum T4 degradation rate (1/hr/kg^0.75).

CLFuI = 0.06;           # Renal clearance rate for iodide (L/hr/kg^0.75).
CLFuP = 0.05;           # Renal clearance rate for perchlorate (L/hr/kg^0.75).
                        # Note that CLuI & CLuP vary as BW0^0.75 in pre-
                        #  pregnancy, but are then multiplied by a BW-
                        #  independent term for changes in pregnancy.

CLuFT4 = 0.001;         # Renal clearance rate for T4 (L/hr/kg^0.75).
CLuFT3 = 0.0027;        # Renal clearance rate for T3 (L/hr/kg^0.75).
                        # Note that CLT4 and CLT3 vary as BW0^0.75, but urinary
                        #  clearance of T4 and T3 (RelimT4 and RelimT3) change
                        # in proportion to the free fractions of T4 & T3, which
                        # vary during pregnancy.

# Permeability values for thyroid, which is diffusion limited.
PAFthy_i = 1.0e-4;      # Diffusion of iodide between thyroid blood and thyroid
                        #  tissue (L/hr/kg^0.75).
PAFthy_p = 1.0e-4;      # Diffusion of perchlorate between thyroid blood and
                        #  thyroid tissue (L/hr/kg^0.75).

# Other parameters.
CT4TAR = 111.8;         # Assumed target steady-state concentration of T4 in
                        #  non-pregnant women (nmol/L).
FRT40 = 1.52e-4;        # Ratio of fT4 to T4 in non-pregnant women.
FRT30 = 0.00279;        # Ratio of fT3 to T3 in non-pregnant women.
bT4 = 0.01845;          # First order term for change in fT4:T4 ratio with
                        #  gestation week.
AobT4 = -0.0778;        # Ratio 2nd order term to 1st order term for change in
                        #  fT4:T4 ratio with gestation week.
TREG = 1.0;             # Boolean flag: 1 for TSH regulation, 0 to turn it off.
pTSHv = 1.0;            # Sensitivity coefficient for TSH regulation effect of
                        #  Vmax for iodine uptake.
pTSHk = 1.0;            # Sensitivity coefficient for TSH regulation effect of
                        #  kprod for T4 & T3 production.
kHCG = 0.00354;         # Sensitivity for hCG-regulation effect (L/kIU).
HCGv = 1;               # Parameter to vary the hCG vs. GA curve for sensitivity
                        #  analysis.
TSHTAR = 1.36;          # "Target" TSH for individual calibration (mIU/L).
                        #  Regulation is neutral (multiplier=1) when TSH =
```

```
                        #  TSHTAR.

# Dosing Parameters.
Pdoseug_i = 0.0;        # Iodide dose rate (ug/d).
Pdosemg_p = 0;          # Perchlorate dose rate (mg/kg/d).

kabsc = 800;            # Scaled first order perchlorate absorption constant
                        #  (kg^0.25/h), Clewell et al. (2007).

# Parameters to be computed in MODEL INITIALIZATION. The values of these
# parameters depend on values of the parameters already defined.
Vpls0 = 0.0;
Vthy0 = 0.0;
QC0 = 0.0;
Qthy0 = 0.0;
Cboundmax = 0.0;
CFT4TAR = 0.0;
TSHhad_1 = 0.0;
TSHhad_2 = 0.0;
TSHhad = 0.0;
TSHCOR = 0.0;
Rdose_i = 0.0;
Pdose_p = 0.0;
dose_ri = 0.0;
eing_g = 0.0;
rdose_pg = 0.0;
t_g = 0.0;
pdose_s = 0.0;
kabs = 0.0;
KdegT4 = 0.0;
KdegT3 = 0.0;
CLT4 = 0.0;
CLT3 = 0.0;

# End of PARAMETERS.
#-------------------------------------------------------------------------------



#-------------------------------------------------------------------------------
# MODEL INITIALIZATION section.
Initialize {
    #
    # Assign an initial value to each state.
    #

    Adose_i = 0.0;          # Amount of iodide dosed (total) (nmol).
    Adose_ri = 0.0;         # ... radioiodide dosed (total) (nmol).
```

```
Astom_ri = 0.0;          # ... radioiodide in the stomach (nmol).
Aplasma_i = 0.0;         # ... iodide in plasma (nmol).
Aplasma_ri = 0.0;        # ... radioiodide in plasma (nmol).
Aelim_i = 0.0;           # ... iodide eliminated (total) (nmol).
Aelim_ri = 0.0;          # ... radioiodide eliminated (total) (nmol).
Arob_i = 0.0;            # ... iodide in the rest-of-body (nmol).
Arob_ri = 0.0;           # ... radioiodide in the rest-of-body (nmol).
AthyB_i = 0.0;           # ... iodide in the thyroid blood (nmol).
AthyB_ri = 0.0;          # ... radioiodide in the thyroid blood (nmol).
Aupthy_ri = 0.0;         # ... radioiodide transported into thyroid (total)
                         #     (nmol).
Abound_i = 0.0;          # ... iodide bound in thyroid tissue (nmol).
Abound_ri = 0.0;         # ... radioiodide bound in thyroid tissue (nmol).
AelimT4 = 0.0;           # ... T4 eliminated (total) (nmol).
AelimrT4 = 0.0;          # ... radio-T4 eliminated (total) (nmol).
AT4 = 0.0;               # ... T4 in the volume of distribution (nmol).
ArT4 = 0.0;              # ... radio-T4 in the volume of distribution (nmol).
AelimT3 = 0.0;           # ... T3 eliminated (total) (nmol).
AelimrT3 = 0.0;          # ... radio-T3 eliminated (total) (nmol).
AT3 = 0.0;               # ... T3 in the volume of distribution (nmol).
ArT3 = 0.0;              # ... radio-T3 in the volume of distribution (nmol).
AIoral_p = 0.0;          # ... perchlorate ingested orally (nmol).
Astom_p = 0.0;           # ... perchlorate in the stomach (nmol).
Aplasma_p = 0.0;         # ... perchlorate in the plasma (nmol).
Aelim_p = 0.0;           # ... perchlorate eliminated (nmol).
Abind_p = 0.0;           # ... perchlorate bound in the plasma (nmol).
ARBC_p = 0.0;            # ... perchlorate in red blood cells (nmol).
Arob_p = 0.0;            # ... perchlorate in the rest-of-body (nmol).
AthyB_p = 0.0;           # ... perchlorate in the thyroid blood (nmol).
AthyT_p= 0.0;           # ... perchlorate in the thyroid tissue (nmol).

#
# Compute parameter values that depend on other paramter values.
#

Vpls0 = VFpls * BW0;     # Initial/pre-pregnancy plasma volume (L).
Vthy0 = VFthy * BW0;     # Initial volume of the thyroid (L).

QC0 = QFC0 * pow(BW0, 0.75);  # Initial cardiac output (L/h).
Qthy0 = QFthy0 * QC0;    # Initial blood flow to thyroid (L/h).

# Maximum concentration of iodide (nmol/L) that can be bound in the
# thyroid. The maximum amount of iodide (nmol) that can be bound in the
# thyroid is found by multiplying this quantity by VthyT, which varies
# with body mass (BW).
Cboundmax = Abndmax0 / (MWI * Vthy0 * VFthyT);

# "Target" free T4 (fT4) concentration (pmol/L) for TSH feedback;
```

```
    # TSH = TSHTAR when CFT4 = CFT4TAR.
    CFT4TAR = FRT40 * CT4TAR * (1.0e3);

    # TSH based on Hadlow (mIU/L). Note that the piecewise function given here
    # is currently hard coded in two places in this file. -- DFK 7-26-17
    TSHhad_1 = exp(1.40 + 3.40/(1.0 + exp((CFT4TAR - 7.01) / 0.971)));
    TSHhad_2 = exp(5.66 / (1.0 + exp((CFT4TAR - 20.3) / 3.05)) - 3.95);
    TSHhad = (CFT4TAR <= 10.7 ? TSHhad_1 : TSHhad_2);
    TSHCOR = TSHTAR / TSHhad;

    # Iodide dose rate (nmol/h).
    Rdose_i = Pdoseug_i * (1.0e3) / (MWI * 24.0);

    # Perchlorate dose rate (nmol/kg/h).
    Pdose_p = Pdosemg_p * (1.0e6) / (MWClO4 * 24.0);

    # First order absorption rate (1/h).
    kabs = kabsc / pow(BW0, 0.25);

    # First order degradation rates for T4 and T3 (1/h).
    KdegT4 = KdegT4F * pow(BW0, 0.75);
    KdegT3 = KdegT3F * pow(BW0, 0.75);

    # Elimination rates for T4 and T3 (L/h).
    CLT4 = CLuFT4 * pow(BW0, 0.75);
    CLT3 = CLuFT3 * pow(BW0, 0.75);
}
# End of MODEL INITIALIZATION.
#-------------------------------------------------------------------------------



#-------------------------------------------------------------------------------
# DYNAMICS section.
Dynamics {
    # ----- Time-varying quantities required for later calculations -----

    # Gestational age in weeks.
    GA =(t - GSTART) / (7.0 * 24.0);
    GA = (GA > 0 ? GA : 0.0);   # Set to zero if GA is non-positive (i.e., if
                                #  t < GSTART).

    # Time-varying body mass (kg). Mass increases with GA.
    BW = BW0 + 0.0065 * (exp(0.68 * (1.0 - exp(-0.087 * GA)) / 0.087) - 1.0);

    # Time-varying elimination rate for iodide (L/h).
    CLuI = CLFuI * pow(BW0, 0.75) * (1.0 + 0.0703 * GA - 0.0012 * pow(GA, 2));

    # Time-varying hematocrit (fraction of blood volume).
```

```
Hct = Hct0 * (1 - 0.001045 * GA - (2.279e-4) * GA * GA
    + (4.475e-6) * pow(GA, 3.0));

# Proportion of T3 and T4 that are free (unbound) (dependent on GA).
# Free/total during gestation defined by ratio of two emperical functions.
T4fun = 1.0 + 0.47 * pow(GA, 7.45) / (pow(8.8, 7.45) + pow(GA, 7.45));
fT4fun = 1.0 + bT4 * GA + bT4 * AobT4 * GA * GA;
FrconvT4 = FRT40 * fT4fun / T4fun;
FrconvT3 = FRT30 * fT4fun / T4fun;

# Amount of free T4 (nmol).
AfT4 = FrconvT4 * AT4;

# Total amount of perchlorate in the thyroid (nmol).
Athy_p = AthyB_p + AthyT_p;

# Permeability values (L/h) for thyroid, which is a diffusion-limited
# compartment.
PAthy_i= PAFthy_i * pow(BW, 0.75);     # ... for iodide.
PAthy_p = PAFthy_p * pow(BW, 0.75);     # ... for perchlorate.

# Human chorionic gonadotropin (hCG) level (kIU/L).
hCGc = 0.013781 * pow(GA, 4.0) - 0.48279 * pow(GA, 3.0) + 4.5866 * GA * GA
    - 4.2849 * GA;
hCG = HCGv * (hCGc > 0 ? hCGc : 0.0);

# Permeability (L/h) for RBCs, which is a diffusion-limited compartment.
PARBC_p = PARBCc_p * pow(BW, 0.75);

# Time-varying elimination rate for perchlorate (L/h). Changes in pregnancy
# are based on GFR(pregnancy)/GFR(control).
CLuP = CLFuP * pow(BW0, 0.75) * (1.0 + 0.029 * GA - 0.0005 * GA * GA);


# ----- Volumes -----

# Time-varying volumes (L) adapted from Gaohua et al. (2012) as described
# in "1T Model Parameters.docx". -- PMS 4-8-17
Vpls = Vpls0 * (1 + 0.001738 * GA + (6.971e-4) * GA * GA
    - (8.893e-6) * pow(GA, 3.0));
VRBC = Vpls * Hct / (1.0 - Hct);

# Volume of thyroid (L) is assumed to vary with total body mass.
# -- PMS 4-17-17
Vthy = VFthy * BW;          # Volume of whole thyroid (L).
VthyB = VFthyB * Vthy;      # Volume of thyroid blood (L).
VthyT = VFthyT * Vthy;      # Volume of thyroid tissue (L).
```

```
# Volume of rest-of-body (L).
Vrob = BW - Vthy - Vpls - VRBC;

# Volume of distribution for T4 and T3 (L).
VDT4  = VDFT40 * (1.0 - 0.0023 * GA) * BW;
VDT3  = VDFT30 * (1.0 - 0.0023 * GA) * BW;


# ----- Blood flow rates -----

# Blood flow rates (L/h). Cardiac output (QC) depends on GA.
QC = QC0 + QCG * (1.0 - exp(-0.1027 * GA));
Qthy = Qthy0 * Vthy / Vthy0;    # ... to thyroid.
Qrob = QC - Qthy;               # ... to rest-of-body.


# ----- Concentrations -----

# Iodide concentrations (nmol/L).
Ca_i = Aplasma_i / Vpls;        # Iodide in plasma.
Crob_i = Arob_i / Vrob;         # ... in rest-of-body.
Cvrob_i = Crob_i / Prob_i;      # ... in veins leaving rest-of-body.
CthyB_i = AthyB_i / VthyB;      # ... in thyroid blood.
Cvtotal_i = (Qrob * Cvrob_i + Qthy * CthyB_i) / QC;
# More iodide concentrations can be found in the "Instantaneous
# equilibration calculations" section below.

# Radioiodide concentrations (nmol/L).
Ca_ri = Aplasma_ri / Vpls;      # Radioiodide in plasma.
Crob_ri = Arob_ri / Vrob;       # ... in rest-of-body.
Cvrob_ri = Crob_ri / Prob_i;    # ... in veins leaving rest-of-body.
CthyB_ri = AthyB_ri / VthyB;    # ... in thyroid blood.
Cvtotal_ri = (Qrob * Cvrob_ri + Qthy * CthyB_ri) / QC;

# Thyroid hormone concentrations (nmol/L).
CT4 = AT4 / VDT4;               # T4 in volume of distribution.
CfT4 = AfT4 / VDT4;             # Free T4 in volume of distribution.
pCfT4 = CfT4 * 1.0e3;           # Ditto (pmol/L).
CrT4 = ArT4 / VDT4;             # Radio-T4 in volume of distribution.
CT3 = AT3 / VDT3;               # T3 in volume of distribution.
CfT3 = FrconvT3 * CT3;          # Free T3 in volume of distribution.
CrT3 = ArT3 / VDT3;             # Radio-T3 in volume of distribution.

# Perchlorate concentrations (nmol/L).
Ca_p = Aplasma_p / Vpls;        # Perchlorate in plasma.
CAbind_p = Abind_p / Vpls;      # ... in plasma proteins (bound).
CAtot_p = Ca_p + CAbind_p;      # ... in plasma and plasma proteins.
CRBC_p = ARBC_p / VRBC;         # ... in red blood cells.
```

```
Crob_p = Arob_p / Vrob;          # ... in rest-of-body.
Cvrob_p = Crob_p / Prob_p;       # ... in veins leaving rest-of-body.
CthyB_p = AthyB_p / VthyB;       # ... in thyroid blood.
CthyT_p = AthyT_p / VthyT;       # ... in thyroid tissue.
Cthy_p = Athy_p / Vthy;          # ... in the whole thyroid (average).
Cvtotal_p = (Qrob * Cvrob_p + Qthy * CthyB_p) / QC;


# ----- Kinetic variables -----

# TSH concentration (mIU/L). Note that the piecewise function given here
# is currently hard coded in two places in this file. -- DFK 7-26-17
TSH_1 = TSHCOR * exp(1.40 + 3.40 / (1.0 + exp((pCfT4 - 7.01) / 0.971)));
TSH_2 = TSHCOR * exp(5.66 / (1.0 + exp((pCfT4 - 20.3) / 3.05)) - 3.95);
TSH = (pCfT4 <= 10.7 ? TSH_1 : TSH_2);

# Maximum rate of NIS transport of iodide into thyroid (nmol/h). This rate
# varies with GA and changes in response to TSH if TREG = 1.
VCHNG = 1.0 + 0.076 * GA - 0.0025 * GA * GA;
TREGv = 1.0 - TREG + TREG * pow((TSH / TSHTAR), pTSHv);
VmaxNIS_thy_i = VmaxNISF_thy_i * pow(BW, 0.75) * VCHNG * TREGv;

# First order production rates for T4 and T3 (1/h).  These change in
# response to TSH if TREG = 1.
HCGREG = 1.0 + hCG * kHCG;
TREGk = 1.0 - TREG + TREG * pow((TSH / TSHTAR), pTSHk);
KprodT4 = KprodT4F * pow(BW0, 0.75) * HCGREG * TREGk;
KprodT3 = KprodT3F * pow(BW0, 0.75) * HCGREG * TREGk;

# Maximum rate of Michaelis-Menten binding of perchlorate to plasma
# proteins (nmol/h).
Vmax_Bp= VmaxC_Bp * pow(BW, 0.75);

# Maximum rate of NIS transport of perchlorate into thyroid (nmol/h).
VmaxNIS_thy_p = VmaxNISF_thy_p * pow(BW, 0.75) * VCHNG * TREGv;

# First order release of perchlorate from plasma proteins (L/hr).
Kunb_p = KunbC_p * pow(BW, 0.75);


# ----- Organified thyroid iodide variables -----

# Maximum capacity for organified iodide in thyroid tissue (nmol).
Aboundmax = Cboundmax * VthyT;

# Amount of unused capacity for organified iodide in thyroid tissue (nmol).
Aremain  = Aboundmax - (Abound_i + Abound_ri);
```

```
# ----- Rates of change -----

# Rate of change of T4 and radio-T4 due to degradation (nmol/h).
RdegT4 = KdegT4 * AT4;
RdegrT4 = KdegT4 * ArT4;

# Rate of change of iodide produced by T4 degradation and radioiodide
# produced by radio-T4 degradation (nmol/h). We assume half of this rate is
# due to complete degradation of T4, which produces 4 units of iodide per
# unit of T4. We assume the other half of this rate is due to conversion of
# T4 to T3, which produces 1 unit of iodide per unit of T4. Thus, on
# average, degradation produces 2.5 units of iodide per unit of T4.
RdeiodT4 = 2.5 * RdegT4;    # = 0.5 * (4.0 * RdegT4 + 1.0 * RdegT4)
RdeiodrT4 = 2.5 * RdegrT4;

# Rate of change of T3 and radio-T3 due to degradation (nmol/h).
RdegT3 = KdegT3 * AT3;
RdegrT3 = KdegT3 * ArT3;

# Rate of change of iodide produced by T3 degradation (nmol/h) and
# radioiodide produced by radio-T3 degradation. Three units
# of iodide are produced per unit of T3.
RdeiodT3 = 3.0 * RdegT3;
RdeiodrT3 = 3.0 * RdegrT3;

# Rate of renal elimination of iodide and radioiodide (nmol/h).
RAelim_i = CLuI * Ca_i;
RAelim_ri = CLuI * Ca_ri;

# Rate of change of radioiodide in stomach (nmol/h). This functionality
# was added to allow for radioiodide bolus dosing. -- DFK 8-2-2017
Rabs_ri = kabs * Astom_ri;
Rstom_ri = -Rabs_ri;

# Rate of change of iodide and radioiodide in plasma (nmol/h). Term for
# rate of absorption (from stomach) has been added to RAplasma_ri.
# -- DFK 8-2-2017
RAplasma_i = QC * (Cvtotal_i - Ca_i) + Rdose_i + RdeiodT4 + RdeiodT3
    - RAelim_i;
RAplasma_ri = QC * (Cvtotal_ri - Ca_ri) + Rabs_ri + RdeiodrT4 + RdeiodrT3
    - RAelim_ri;

# Rate of change of iodide and radioiodide in rest-of-body (nmol/h).
RArob_i = Qrob * (Ca_i - Cvrob_i);
RArob_ri = Qrob * (Ca_ri - Cvrob_ri);

# Rate of NIS transport of iodide and radioiodide into thyroid (nmol/h).
```

```
RNISthy_i = VmaxNIS_thy_i * CthyB_i / (CthyB_i + CthyB_ri
    + KmNIS_i * (1.0 + CthyB_p / KmNIS_p));
RNISthy_ri = VmaxNIS_thy_i * CthyB_ri / (CthyB_i + CthyB_ri
    + KmNIS_i * (1.0 + CthyB_p / KmNIS_p));

# Rate of production of T4 and radio-T4 (nmol/h).
RprodT4 = KprodT4 * Abound_i;
RprodrT4 = KprodT4 * Abound_ri;

# Rate of iodide usage for the production of T4 (nmol/h). Producing 1 mol
# of T4 requires 4 mol of iodide.
RioduT4 = 4.0 * RprodT4;
RiodurT4 = 4.0 * RprodrT4;

# Rate of production of T3 and radio-T3 (nmol/h).
RprodT3 = KprodT3 * Abound_i;
RprodrT3 = KprodT3 * Abound_ri;

# Rate of iodide usage for the production of T4 (nmol/h). Producing 1 mol
# of T3 requires 3 mol of iodide.
RioduT3 = 3.0 * RprodT3;
RiodurT3 = 3.0 * RprodrT3;

# Rate of elimination of T4 and radio-T4 (nmol/h).
RelimT4 = CLT4 * CT4 * FrconvT4 / FRT40;
RelimrT4 = CLT4 * CrT4 * FrconvT4 / FRT40;

# Rate of change of T4 and radio-T4 in the volume of distribution (nmol/h).
RT4 = RprodT4 - RdegT4 - RelimT4;
RrT4 = RprodrT4 - RdegrT4 - RelimrT4;

# Rate of elimination of T3 and radio-T3 (nmol/h).
RelimT3 = CLT3 * CT3 * FrconvT3 / FRT30;
RelimrT3 = CLT3 * CrT3 * FrconvT3 / FRT30;

# Rate of change of T3 and radio-T3 in the volume of distribution (nmol/h).
RT3 = RprodT3 + 0.5 * RdegT4 - RdegT3 - RelimT3;
RrT3 = RprodrT3 + 0.5 * RdegrT4 - RdegrT3 - RelimrT3;

# Rate of ingestion of perchlorate (nmol/h). "Ingested" perchlorate is
# assumed to go straight into the plasma (not the stomach).
RAIoral_p = Pdose_p * BW;

# Rate of change of perchlorate in stomach (nmol/h).
Rabs_p = kabs * Astom_p;
Rstom_p = -Rabs_p;

# Rate binding to plasma proteins of perchlorate (nmol/h).
```